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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,813	04/08/2004	Thomas A. Boyd	P0453.70112US01	9059

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	**PAPER NUMBER**
1614	

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06/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,813	BOYD ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,14-32,38,39,42,44,45,51-70,76,77,82-85,88,93,95,96,103,104 and 107-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-18-08;3-28-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4-18,21-33,35,36,38-40,43,45,48-61,64-79,82-85,88,91-96,98,100-109 and 112-121.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 2,4-10,12,13,33-37,40,48-50,71-75,78,79,89-92,94,97-102,105 and 106.

Applicants' Amendment filed March 18, 2008 is acknowledged. Claims 19, 20, 34, 37, 62, 63, 89, 90, 97, 99, 110 and 111 are canceled. Claims 2, 4-10, 12, 13, 33, 35, 36, 40, 48-50, 71-75, 78, 79, 91- 94, 98, 100-102, 105 and 106 remain withdrawn from consideration. Accordingly, claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 are now under consideration.

Information Disclosure Statements filed March 18, 2008 and March 28, 2008 are acknowledged and have been reviewed to the extent each publication is provided. Seven co-pending applications, and PCT/US04/10996, are further noted.

Applicants' arguments have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are reiterated. They constitute the complete set presently applied to the instant application.

In the last Office Action claims 1, 11, 14-32, 38, 39, 42, 43, 51, 56-70, 76, 77, 113 and 115 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. It was asserted the claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite treating a patient with a symptom of constipation-predominant irritable bowel syndrome (IBS) comprising administering methylnaltrexone, and, in particular, various subsets of patient populations, various symptoms of IBS and administration of multiple drug therapy. Passages from The Merck Index were provided to show the state of the art with respect to various subsets of patient populations (page 313), various symptoms of IBS

(pages 312-313) and administration of multiple drug therapy (pages 314-315). There is insufficient written basis for the subject matter of the claims. This is a Written Description rejection.

Applicants cite various passages throughout the specification and urge compliance with the enablement requirement is met.

Example 1, pages 14-15, is drawn to the administration of methylnaltrexone in subjects who are **not** suffering from irritable syndrome. Applicants argue a significant reduction of gut transit time suggests a treatment for irritable bowel syndrome. A reduction of gut transit time would have reasonably been correlated with diarrhea-predominant irritable bowel syndrome. With respect to the other citations in the specification to which Applicants refer, only background information related to irritable bowel syndrome and dosage regimens and drug formulations are provided. Applicants' disclosure fails to show a method of treating a patient with a symptom of constipation-predominant irritable bowel syndrome.

At best treatment regimens are prophetic. Applicants have not conveyed possession of the invention with reasonable clarity to one skilled in the art. The disclosure lacks sufficient written description for all claimed limitations. Sufficient guidance to support predictable operability of the invention to one of ordinary skill in the art is absent. The rejection of record of claims 1, 11, 14-18, 21-32, 38, 39, 43, 51, 56-61, 64-70, 76, 77, 113 and 115 under 35 U.S.C. 112, first paragraph, is maintained.

Claims 88, 93, 95, 96, 103, 104, 107-114 and 116-121 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-29, 32, 33 and 39-44 of copending Application No. 11/441452 because the copending application

is drawn to pharmaceutical compositions comprising methylnaltrexone, optionally in combination with other therapeutic agents, as well as in the same dosages forms that are recited in the present claims.

It is noted claim 66 in Application S.N. 11/441452 is drawn to the treatment of irritable bowel syndrome. Various claims in co-pending application S.N. 11/441395 are also drawn to the treatment of irritable bowel syndrome and treating constipation, as well as to compositions comprising methylnaltrexone.

Applicants choose to hold the provisional double patenting rejection in abeyance.

The rejection of record on the ground of nonstatutory obviousness-type double patenting is maintained.

Claims 1, 11, 14-27, 29-32, 38, 39, 42, 44-5, 51-68, 70, 76, 77, 82-85, 88, 93, 5, 96, 103, 104, 107, 108 and 110-120 were rejected under 35 U.S.C. 103(a) as being unpatentable over Levine, J.D., US 2004/0180916, in view of The Merck Manual, and De Schryver et al., Scand. J. Gastroenterology, in the last Office Action. It was asserted Levine teaches the administration of the specific μ opioid antagonist methylnaltrexone in combination with a κ-opioid receptor agonist to treat pain associated with IBS. As required by instant claims 29 and 31, an opioid agonist is simultaneously administered to a patient. See, for example, page 18, paragraph [0120]. No occurrence of calcium or salts thereof is noted in the Levine document. No restriction is noted among male, female or child patients. The open language of the present claims allows for the inclusion of any number of additional active agents. Benzodiazepines (antidepressants) are included among those κ-opioids contemplated. See, for example, claim 148, as required by instant claims 30, 32, 70, 88 and 115. Psychological stress and anxiety are

factors in the exacerbation of IBS and administration of a benzodiazepine, an anti-anxiety agent, may be a component of therapy for IBS. As required by instant claims 11, 14, 52-55, 103, 104 and 107, various dosage forms are disclosed on pages 16-18. As required by instant claim 55, direct mucosal administration is disclosed on page 34, claim 154. As required by instant claim 52-54 and 104, enteric-coated formulations and sustained-release formulations are disclosed on pages 16, paragraph [0103], and page 18, paragraph [0116]. As required by instant claim 108, pharmaceutical kits (with instructional materials) are described on page 1, paragraph [0003], and on page 25, paragraphs [0159] and [0160]. Dosage ranges, generally, 0.02 mg to 8 mg, as required by instant claims 82-84, are taught by Levine on page 6, paragraphs [0037] and [0038]. Levine fails to distinguish various subsets of patient populations, various symptoms of IBS and administration of additional drugs that are 5-HT_4 agonists.

However, The Merck Index teaches various subsets of patient populations (page 313), various symptoms of IBS (pages 312-313) and administration of multiple drug therapy (pages 314-315). Signs and symptoms of IBS include pain, abdominal distention and abnormal bowel function. There are two major clinical types of IBS: constipation-predominant and diarrhea-predominant. Men, women and children are known to present distinct signs and symptoms and to respond to medications differently. Drug therapy is supportive and palliative and includes increasing dietary fiber, anticholinergic drugs and specific agents to treat either diarrhea or constipation. As disclosed by The Merck Index, combination drug therapy in the treatment of IBS is conventional. Abdominal bloating, pain and distention, and abnormal stools characterize IBS.

Levine fails to teach administration of methylnaltrexone with an additional irritable bowel syndrome therapeutic agent. However, De Schryver teaches the administration of the selective $5HT_4$ agonist tegaserod, as required by instant claims 76, 77, 85, 95, 96, 112-114.

Applicants argue the earliest publication date of Levine is September 16, 2004 with respect to the administration of methylnaltrexone to treat pain associated with irritable bowel syndrome.

Although Provisional Application 60/433,217 fails to recite methylnaltrexone among the μ opioid antagonists that are administered in combination with a κ-opioid receptor agonist to treat pain associated with IBS, Levine specifically recites naltrexone, naloxone and nalmefene, other μ opioid antagonists all, of which are structurally similar. Because methylnaltrexone does not cross the blood brain barrier, motivation is provided to select methylnaltrexone in place of naltrexone.

Therefore, based on the priority date of December 13, 2002 of Levine's provisional application, the reference remains prior art. The rejection of claims 1, 11, 14-18, 21-27, 29-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 93, 95, 96, 103, 104, 107, 108 and 110-120 is maintained under 35 U.S.C. 103(a), as being unpatentable over Levine, J.D., US 2004/0180916, in view of The Merck Manual, and De Schryver et al., Scand. J. Gastroenterology.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this Final Action is set to expire THREE MONTHS from the mailing date of this Action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this Final Action and the Advisory Action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the Advisory Action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the Advisory Action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this Final Action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 6, 2008

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614